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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,027	07/30/2007	Axel Bouchon	BHC 03 2001	5506

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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
01/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,027	BOUCHON ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *5, 17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/EP04/11008 filed 10/02/2004 which claims priority to EPO 03023288.8 filed 10/15/2003; EPO 03023287.0 filed 10/15/2003; EPO 03025573.1 filed 11/08/2003; and EPO 03025572.3 filed 11/08/2003.

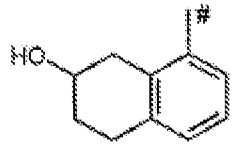
Claims 1-22 are pending. Claims 5, 17-22 are withdrawn from consideration. Claims 1-4, 6-16 are under examination.

Claim Rejections/Objections Withdrawn

2. The rejection of claims 1, 6-16 under 35 U.S.C. 112, second paragraph, as being indefinite for what is apparently an extra carbon on both the E groups and the A groups (the tetrahydronaphthylene ring) is withdrawn. Based on the application as a whole and the statements of counsel this is just a bond and not another carbon. The record is now clear.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

3. The rejection of claims 8-16 under 35 U.S.C. 112, second paragraph, as being indefinite for the functional language is maintained. The rejection of claims 1-2, 6-16 under 35 U.S.C. 112, second paragraph, as being indefinite for the reference to a "Chapter" is maintained. The rejection of claims 1-4, 6-16 under 35 U.S.C. 102(e) as being anticipated by WO03095420 (cited on the IDS, also made over the PGPub of U.S. application 10/513,848 the national stage), is maintained. Applicant's representative has argued that the proviso removes these anticipatory compounds, because the various "Chapter" designation provios remove these compounds as prior art. These "Chapter" designations are not understandable, and has been rejected under 112 2nd, however assuming arguendo that they removed the compounds with various Q's which would make a tetrahydronaphthalene, the second option for A, shown here:



does not require any Q's. This structure is drawn in dependent claims as well. Clearly the claims read on the prior art in numerous ways and Q selection or "Chapter" reading is not required.

The rejection of claims 1-2, 6-16 under 35 U.S.C. 103(a) as being unpatentable over Aman JP 04178362 A and Aman JP 04178363 is maintained. The rejection of claims 1, 6-16 under 35 U.S.C. 103(a) as being unpatentable over Pevarello U.S. 6,863,647 is maintained. The applicant's representative has argued that the examiner failed to show that a change such as H to Me was obvious. See In Re Herr 134 USPQ 176 (C.C.P.A. 1962), finding the presence of a methyl group failing to create a patentable distinction over the prior art ("The only structural distinction in appellant's compounds over those of Herr et al. is the presence of a methyl group in the 17 position of the claimed compounds. It is noted that the two compounds used as standards in the art have exactly the same structural difference. It therefore appears, as the board held, that the 17-methyl derivative of Herr et al. would be an obvious structural change to a chemist of ordinary skill in that field.") See also In re Wood, Whittaker, Stirling, and Ohta, 199 USPQ 137 (C.C.P.A. 1978) and In re Lahr, 137 USPQ 548, 549 (C.C.P.A. 1963). Also discussed as an ancillary issue in In Re Paquette 165 USPQ 317, "we also think it would be obvious to the person skilled in the art to provide dimers of an N-methyl-2-pyridone modified by the presence of a methyl substituent on one of the otherwise unsubstituted carbons of the ring. Since little

could be more expected than that the resulting dimer would have two such substituents, that fact clearly does not detract from the obviousness of claims 15-18."

The rejection of claims 1-3, 6-16 under 35 U.S.C. 103(a) as being unpatentable over Olesen et. al. WO 9422807 AND Christophersen et. al. WO 9745111 (abstract only) in view of Patani et. al. *Chemical Reviews* 1996, 96, 3147-3176 AND Gross WO 9937607 is maintained. Applicant's representative is arguing limitations not present in the claims, i.e. the Chapter designations and provisos do not remove these references as prior art. Contrary to the statement "the claimed compounds require more than substitution of the tetrahydronaphthylene compounds by a hydroxyl group." they actually do not require more than that.

The rejection of claims 1-4, 6-16 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Contrary to the statement that "The examiner provides no basis why one skilled in the art could not make the full scope of compounds of formula I, test the pharmacological activity of these compounds, prepare pharmaceutical compositions with these compounds, and administer these compounds." the rejection cites two articles that show a heightened degree of unpredictability in the development of TRPV1 ligands. Minor changes lead to compounds that no longer have this activity. The scope claimed simply will not function as TRPV1 ligands. While working examples are not required, in nascent technologies such as the instant case the degree of unpredictability is an important factor. In order to practice the full scope of the invention, one of ordinary skill would not only need to create synthetic procedures *de novo*, but also decide what compounds to prepare. The specification gives little guidance with regard to what the requirements for activity are i.e. which substituents lead to activity. It is the conclusion of the examiner as shown by the state of the art in the TRPV1 drug development art

that the full scope of the claims is not enabled. The examiner's position is that the examples do not support the genus as claimed. In response to the inconsistency of the rejection with established case law, the examiner respectfully disagrees. Rejections of this type have a long history.

In re Fouche 169 USPQ 429 dealt with a similar issue with respect to how to use requirement of 112 1st paragraph,

"Both the examiner and the board noted that none of the working examples pertained to compounds wherein Z was heterocyclic. Appellant is quite correct in contending that, under our decisions in In re Robins, 57 CCPA 1321, 429 F.2d 452, 166 USPQ 552 (1970), the inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention. Nevertheless, an applicant must use some technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art. It seems clear, and it is not disputed by appellant, that where an applicant undertakes to define his invention by the recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of the Markush group."

Clearly the Markush group is not supported by a working example for each member.

The examiner is not holding the applicant to a rigid scientific standard based in scientific fact, but rather the standard of patent law that the scope of the claims should be commensurate in scope with the invention disclosed. The groups rejected in the instant claims are entirely prophetic. The examiner submits that while some modifications to the instantly claimed compounds are possible, this is an area that might be explored in future research, but has not been explored here. The determination of these relationships and the discovery of potent analogs is a different invention, and one that the applicant has not shown to be in possession of. While the examiner would not reject small, modest changes such as the addition of a methyl group or halogen, the instant claims recite substituents that go far beyond even specious scientific

reasoning. In fact the scope is unclear, hence the 112 2nd rejections. In this case the claims bear little structural resemblance to the exemplified compounds, which are relatively homogenous and non-representative of the scope claimed. No trail is blazed to support the instantly claimed genus or guide the skilled artisan to some particular area where experimentation might take place.

See *Ex parte WEIL AND SCHLICHTING*, 158 USPQ 620 (Bd. Pat. App. & Int. 1967)

"We will sustain this rejection of the claims as we are in accord with the examiner's position. We find no support in the disclosure for such compounds encompassed by these claims wherein R 1, R 2, R 3, and R 5are all the same and selected from the group, lower alkyl , hydroxy , alkoxy , di(loweralkyl)amino and nitro for example. These claims appear to be in the nature of a paper concept wherein all possible substituents have been included in the composition. There are no examples of such compounds which are included within the vast scope encompassed by these claims, although appellants have a considerable disclosure with respect to certain components but this does not warrant claims of the enormous breadth recited. Many of the starting materials are non-existent and while appellants have presented broad processes for making some of the starting materials, it is not clear that all starting materials encompassed by the broad claims may be made from the disclosure presented. We are, therefore, in accord with the examiner's position that these claims are too broad and insufficiently supported by the disclosure."

See *Ex parte Herzog, Hershberg, and Coan*, 115 USPQ 195 (Bd. Pat. App. & Int. 1956) affirming the examiner, and stating "it becomes obvious that the expressions defining the organic acids used.....are inclusive of inoperative materials and go far beyond the adequately disclosed subject matter of the specification."

And also *Ex parte DIAMOND,* 123 USPQ 167 (Bd. Pat. App. & Int. 1959) where the examiner was affirmed for a scope of enablement rejection, and the court stated:

"the specification contains 23 specific examples, but it will be noted that they are to the preparation of relatively simple compounds.....This must be regarded as a relatively meagre and nonrepresentative disclosure to support claims which embrace millions of compounds. It should also be observed that appellant is working in a field where little prediction is possible and this Board has on several occasions held that the scope of claims should not be unduly extensive in fields where applicability is highly speculative or not explored and that subject matter which relies upon prediction for its support is unpatentable. Ex parte Middleton, 87 USPQ 57 ; Ex parte Kauck et al., 95 USPQ 197 , Ex parte Rosenkranz et al., Pat. No. 2,715,637. In Minnesota Mining and Mfg. Co. et al. v. Carborundum Co. et al., 155 F.2d 746, 69 USPQ 288 , the court

held that 'An inventor cannot disclose a small number of components which will serve as a springboard for claiming an entire class.'"

See also: *Schering Corporation v. Gilbert et al.*, 68 USPQ 84 (2d Cir. 1946)

"Theoretically a multitude of substances not as yet found in nature and not as yet compounded could be synthesized, if skilled organic chemists were given the time and materials with which to work, and actually the formulas for them could be written. There is, however, a practical limit upon synthesis, though the extent of that is not fully known, for some of the new theoretical compounds might be impossible to create, and some would be so unstable that they would disintegrate either at once or in short periods of varying length. Moreover, while analogy is at times useful, organic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected."

And *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976)

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

In re Prutton, 96 USPQ 147 (C.C.P.A. 1952)

"The complete list of organic compositions includes, in generic form, most of the organic compounds found discussed in ordinary textbooks of organic chemistry..... It appears to be appellant's view that a selection of an unsaturated hydrocarbon from the first list and of a sulphide of phosphorus from the second list will provide support for the claims here under discussion. The Examiner holds, and properly we think, that the presentation of such lists from which reagents may be selected is not a sufficient disclosure to support claims to a particular class of reaction product which might be produced by proper selection of reagents and determining the conditions of reaction."

In re Walker, 22 USPQ (C.C.P.A. 1934)

"It is true, as argued by counsel, that appellant is entitled to claim not only the substance enumerated by him in his specification, but also their equivalents. However, in cases of this character, involving chemicals and chemical compounds, many of which of course differ radically in their properties, it must appear in the specification, either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that "the chemicals or chemical combinations included therein were generally capable of accomplishing

the desired result." See *In re Ellis*, 37 App. D. C. 203; *In re Dosselman*, 37 App. D. C. 211; *In re Langmuir*, 20 C. C. P. A. (Patents) 733, 62 F. (2d) 93."

A case directly on point is *In Re Sus and Schaefer* 134 USPQ 1962 301-310 (*affirmed*):

"It is, however, consistent with this public purpose embodied in the pertinent statutory requirement that the *invention claimed* shall be no broader than the *invention set forth* in the written description forming a part of the specification……thus it seems to us that one killed in this art would not be taught by written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only *certain aryl radicals* and certain specifically substituted aryl radicals would be suitable for such purposes." Emphasis in Original.

This application contains claims drawn to a nonelected invention with traverse. A complete reply to this Final action must include a cancellation of nonelected claims or other appropriate action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 8-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It would appear that these claims are compositions, despite the recitation of functional language "is a VR1 antagonist" "for the treatment and/or prevention of" various symptoms and disease, etc. as they are drawn to the same materials. Functional language as that of the instant claims carries no patentable weight in claims for compositions of matter see *Union Oil Co. of California v. Atlantic Richfield Co.* 54 USPQ2d 1227 where "composition claims

cannot, as the appellant refiners argue, embrace only certain uses of that composition. (citing In Re Spada) Otherwise these composition claims would mutate into method claims." The scope of these claims is unclear as one cannot ascertain based on the structure of the compounds of claim 1 which materials actually meet the requirements of these various limitations. These compounds have not been evaluated for any therapeutic use. Should the applicant want to pursue method claims in this application they will be rejoined to allowable product claims. It is recommended that these claims be rewritten without intended use.

4. Claims 1-2, 6-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The reference to a "Chapter" has no antecedent basis. It is unclear what these representations mean as chemical language does not use "Chapter". Moreover the variables are continuously redefined with these "Chapter" designations such that it is unclear what is actually being claimed.

Claim Rejections - 35 USC § 102

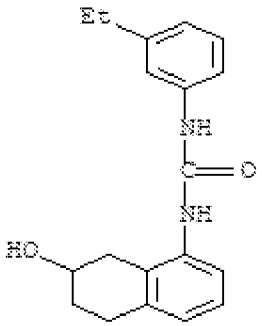
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

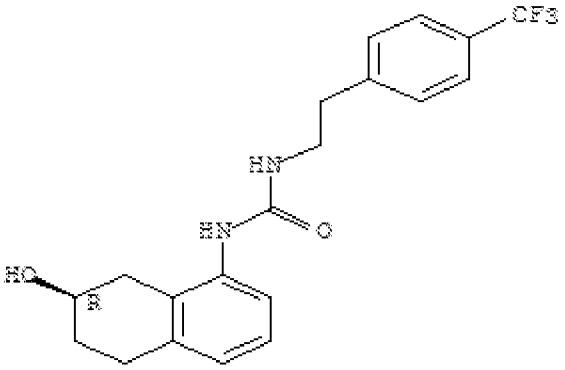
> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5 Claims 1-4, 6-16 are rejected under 35 U.S.C. 102(e) as being anticipated by WO03095420 (cited on the IDS, also made over the PGPub of U.S. application 10/513,848 the

national stage), which has a common assignee and some common inventors with the instant application.

The WO document teaches hundreds of anticipatory compounds such as those shown below, where A is the hydroxynaphthalenes and E is various urea and amide moieties. This is essentially the genus of claims 1-4.





Claim Rejections - 35 USC § 103

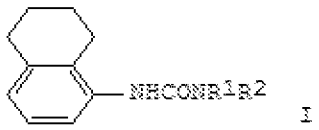
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-2, 6-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aman JP 04178362 A and Aman JP 04178363. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

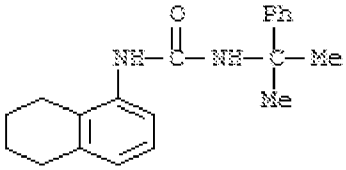
A) Aman et. al. teaches a class of compounds that are antifungals, acaricides, miticides etc. In particular the following genus of compounds:

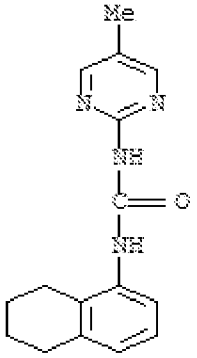


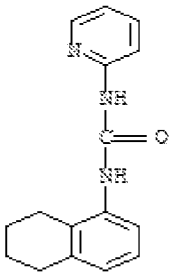
I

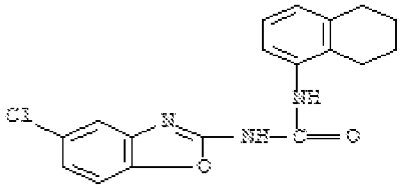
Urea derivs. I [R1 = H, lower alkyl, lower alkoxy; R2 = lower alkyl, lower alkenyl, 4-morpholinyl, (lower alkoxycarbonyl-, carbamoyl-, or arylcarbonyl-substituted) Ph, five-membered heterocyclyl, etc.]

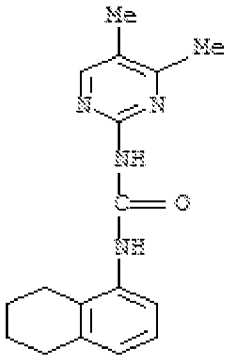
Some examples provided to support this genus are shown below:

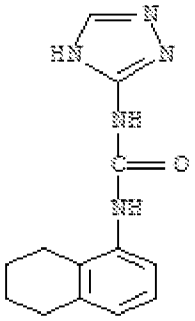


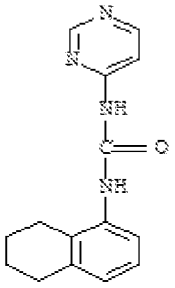


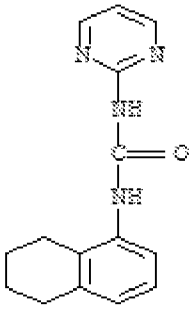


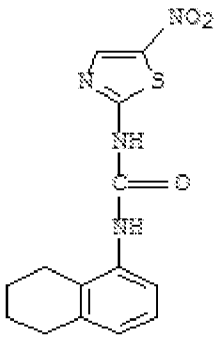


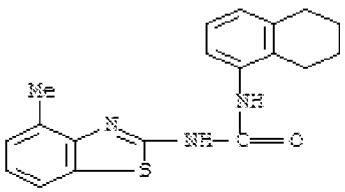


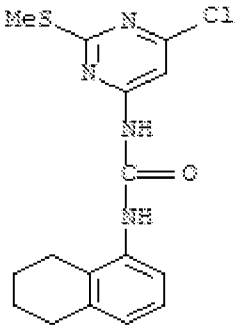


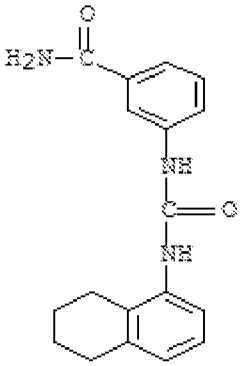


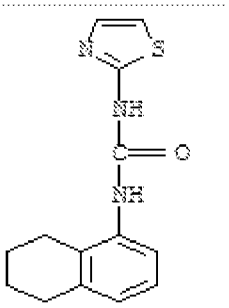


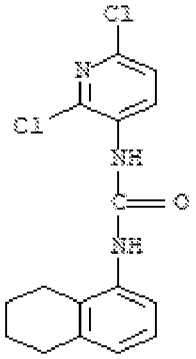


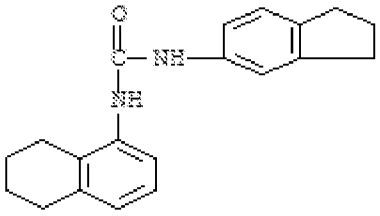


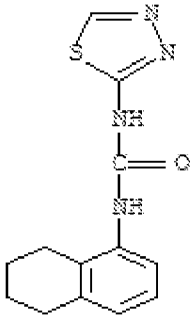


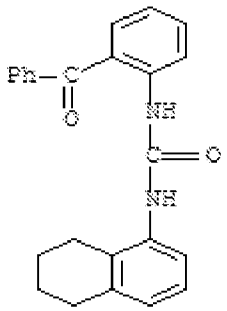


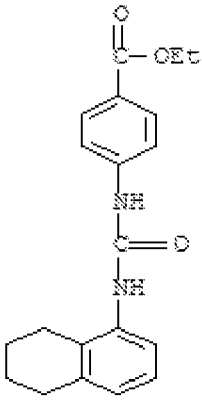


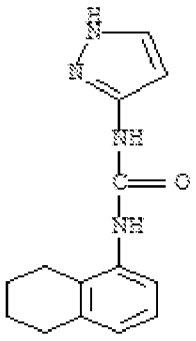


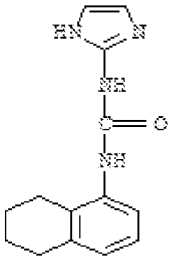


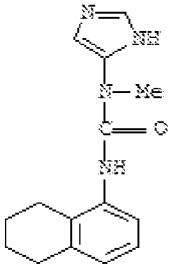


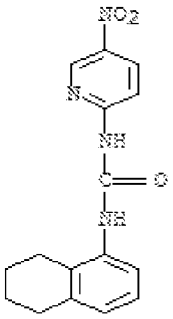












B) While the instant claims have provisoed out the prior art species the only difference at least when R^2 or R^3 is alkyl is the interchange of H for methyl.

C) The level of ordinary skill in the art is high, and would be someone with synthetic chemistry experience and biochemistry. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these analogs based on the expectation that such simple analogs would have similar properties and upon the routine nature of such experimentation.

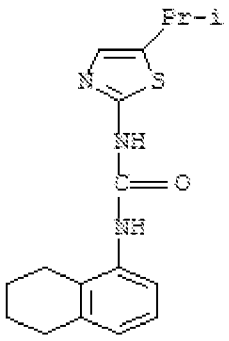
D) In at least one aspect the only difference is H vs. Me, which has long been held to be a non-patentable distinction. (See *In Re Herr* 134 USPQ 176, *In re Wood*, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and *In re Lahr*, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963), also discussed in *In Re Paquette* 165 USPQ 317, "we also think it would be obvious to the person skilled in the art to provide dimers of an N-methyl-2-pyridone modified by the presence of a methyl substituent on one of the otherwise unsubstituted carbons of the ring. Since little could be more expected than that the resulting dimer would have two such substituents, that fact clearly does not detract from the obviousness of claims 15-18." See also *Ex parte Bluestone*, 135 USPQ 199 (Bd. Pat. App. & Int. 1961) finding that the N-methyl derivative of a prior art thiazolidinone unpatentably obvious and stated, citing *Ex parte Weston and Hamlin* with favor "A case nearly on all fours with this situation is *Ex parte Weston and Hamlin*, 121 USPQ 428 , wherein this Board held that mono substituted N' piperazines were not patentable over di-substituted piperazines of the reference because chemists are well aware of the difference between secondary and tertiary amines and their reactivities including the possibility of further substitution for the hydrogen in the secondary amine. This is the substitution that appellant has made in the Alvord compound." *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34

USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para)*. In terms of the composition claims, the compounds were dissolved in DMSO, which is a pharmaceutically acceptable solvent.

7. Claims 1, 6-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pevarello U.S. 6,863,647. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) U.S. 6,863,647 teaches a class of compounds that were useful as cdk/cyclin inhibitors, and are useful for treating cell proliferative disorders. In particular the following compound:

RN 267430-46-6 CAPLUS
CN Urea, N-[5-(1-methylethyl)-2-thiazolyl]-N'
naphthalenyl)- (CA INDEX NAME)



B) While the instant claims have provisoed out the prior art species the only difference at least when R1 or R is heteroaryl and the heteroaryl is thiazole and R^2 or R^3 is alkyl is the interchange of H for methyl.

C) The level of ordinary skill in the art is high, and would be someone with synthetic chemistry experience and biochemistry. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these analogs based on the expectation that such simple analogs would have similar properties and upon the routine nature of such experimentation.

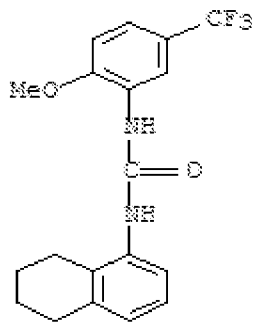
D) In at least one aspect the only difference is H vs. Me, which has long been held to be a non-patentable distinction. (See *In Re Herr* 134 USPQ 176, *In re Wood*, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and *In re Lahr*, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963), also discussed in *In Re Paquette* 165 USPQ 317, "we also think it would be obvious to the person skilled in the art to provide dimers of an N-methyl-2-pyridone modified by the presence of a methyl substituent on one of the otherwise unsubstituted carbons of the ring. Since little could be more expected than that the resulting dimer would have two such substituents, that fact clearly does not detract from the obviousness of claims 15-18." See also *Ex parte Bluestone*, 135 USPQ 199 (Bd. Pat. App. & Int. 1961) finding that the N-methyl derivative of a prior art thiazolidinone unpatentably obvious and stated, citing *Ex parte Weston and Hamlin* with favor "A case nearly on all fours with this situation is *Ex parte Weston and Hamlin*, 121 USPQ 428 , wherein this Board held that mono substituted N' piperazines were not patentable over di-substituted piperazines of the reference because chemists are well aware of the difference between secondary and tertiary amines and their reactivities including the possibility of further substitution for the hydrogen in the secondary amine. This is the substitution that appellant has made in the Alvord compound.") *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34

USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para)*. In terms of the composition claims, the compounds were tested for pharmacological activity in a pharmaceutically acceptable solvent.

8. Claims 1-3, 6-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olesen et. al. WO 9422807 AND Christophersen et. al. WO 9745111 (abstract only) in view of Patani et. al. *Chemical Reviews* 1996, 96, 3147-3176 AND Gross WO 9937607. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

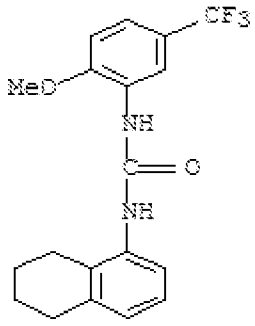
A) Olesen et. al. WO 9422807 teaches a class of compounds that were useful as ion channel inhibitors, and are useful for treating arterial hypertension, coronary artery spasms, asthma, irritable bowel syndrome, spastic bladder, ischemia, psychosis, convulsions. In particular WO 9422807 the following compound:

RN 160383-97-1 CAPLUS
CN Urea, N-[2-methoxy-5-(trifluoromethyl)phenyl]-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)- (CA INDEX NAME)

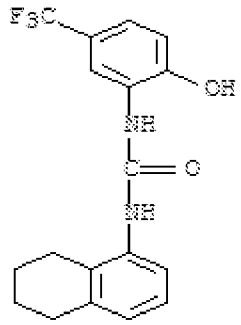


WO 9745111 teaches the following compounds:

CN Urea, N-[2-methoxy-5-(trifluoromethyl)phenyl]-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)- (CA INDEX NAME)



RN 200267-58-9 CAPLUS
CN Urea, N-[2-hydroxy-5-(trifluoromethyl)phenyl]-N'-(5,6,7,8-tetrahydro-1-naphthalenyl)- (CA INDEX NAME)



B) The difference between the prior art and the instant claims is a hydroxy group.

C) The level of ordinary skill in the art is high, and would be someone with synthetic chemistry experience and familiar with biochemistry. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these analogs

based on the expectation that such simple analogs would have similar properties and upon the routine nature of such experimentation.

D) The replacement of a hydrogen atom with a hydroxy group is a well known modification in medicinal chemistry as shown by Patani Pg. 3152, at "4. Fluorine and Hydroxyl, Amino, or Methyl Groups as Replacements for Hydrogen (Grimm's Hydride Displacement Law)". Most compellingly, the Gross document show that in the field of ion channel ligand development, hydroxylation of the tetrahydronaphthalene nucleus is well known, see the entire document, the table on pg. 29 for instance. The tetrahydronaphthalene nucleus is hydroxylated in this very precise 2 position.

One would be motivated to make this change with the expectation that the compounds would be ion channel ligands and a further expectation that potency would be increased. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para).* In terms of the composition claims, the compounds were tested for pharmacological activity in a pharmaceutically acceptable solvent. Given the very close utility, structural similarity and the fact that this modification was well known in this very narrow field the conclusion of obviousness is appropriate.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-4, 6-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds where R^1, R^4, or R is phenyl, benzyl, CH_2-pydridyl, 1,3-benzodioxolyl, tetrahydronaphthalene, isoxazole, dihydroindene, thiadiazole and indole which could be substituted with halogen, CF_3, OCF_3, phenyl, pyridine, pyridyloxy, alkoxy, and alkyl, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of substituted phenyl derivatives, heterocycles, and amines bearing multiple substitutions of an unascertainable scope see 112 2nd rejection above. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. In addition these compounds are claimed to be used as drugs. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist who would make the compounds. **(C) The state of the prior art: (E) The**

level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:

The applicant has given the public little guidance as to what the requirements of activity for these compounds might be. The sole statement we are given: "For practical reasons, the compounds are grouped in four classes of activity as follows: IC50- A < or = 0.11μM B < or = 0.5μM C < or = ~ 1μM < D." It is known that structural requirements exist for TRPV1 ligands. In a similar class of compounds substitution of *t*-Bu on an aromatic ring adjacent to the amide with OMe had a 1000 fold decrease in activity (Michele C. Jetter, Mark A. Youngman, James J. McNally, Sui-Po Zhang, Adrienne E. Dubin, Nadia Nasserb and Scott L. Dax, "N-Isoquinolin-5-yl-N0-aralkyl-urea and –amide antagonists of human vanilloid receptor 1 *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 3053–3056; Table 1, compare **7l** to **7n**). Thus electron withdrawing or at least lipophilic groups seem to be required for activity. The compounds of broad claims of 1-4, 6-16, would not work as antagonists.

More informatively, a large SAR study was done on TRPV1 antagonist remarkably similar to the compounds of the instant case, which no doubt benefited the design of the instant invention, Swanson et. al. "Identification and Biological Evaluation of 4-(3-Trifluoromethylpyridin-2-yl)piperazine-1-carboxylic Acid (5-Trifluoromethylpyridin-2-yl)amide, a High Affinity TRPV1 (VR1) Vanilloid Receptor Antagonist" *Journal of Medicinal Chemistry* **2005**, 48, 1857-1872. In this study it was found that the heterocyclic moiety must be a piperidine, or piperazine:

> "The first library (Figure 1) demonstrated the desirability of an electron-withdrawing group in the para position of the aniline fragment for antagonist

activity and suggested that 3-substituted pyridin-2- ylpiperazines were favored. In the second library (Figure 2) which contained no 3-substituted pyridines only low affinity agonists and antagonists were obtained. The third library (Figure 3) was most informative and clearly demonstrated the importance of a 3-substituted pyridin- 2-ylpiperazine (3-Cl, 3-CH3, and 3-CF3) and a *p*-trifluoromethyl group in the aniline fragment. A fourth library, not shown, prepared from aliphatic isocyanates and 3-substituted pyridin-2-ylpiperazines afforded only inactive compounds, suggesting the need for an aromatic urea. With the intrinsic activity of the pyridinylpiperazine template confirmed, we turned our attention to a more thorough investigation of SAR at the human receptor via targeted synthesis. To this end, specific changes to the pyridine, piperazine, and aniline fragments were made. When the pyridine point of attachment was examined, 17 and 18, it was immediately apparent that the pyridin-2-ylpiperazine was optimal. A range of modifications to or replacements for the piperazine (20-26) showed that the piperazine ring was tolerant of small substituents (e.g. 20) but further substitution (21-23), ring expansion (24) or replacement with 3-aminopyrrolidine (25) or 4-aminopiperidine (26) afforded considerably less active compounds. Removal of a single piperazine nitrogen (27 and 28), using the chemistry of Scheme 2, afforded a less active compound as did removal of both a piperazine and the pyridine nitrogens, using the chemistry of Scheme 3 (29 and 30)."

Compounds 23 and 25, are inactive, not less active, but inactive.

Table 1. Potency at Recombinant TRPV1[a]

compd	human EC_{50} (nM)	efficacy (%)	human IC_{50} (nM)	SEM (*n*)	rat EC_{50} (nM)	efficacy (%)	rat IC_{50} (nM)
23			>10000	(3)			>10000
25	>10000, IA[b]		>10000	(3)			13100

What are the important structural features for the claimed utility? The compounds that were prepared at least, a lipophilic substituents of limited size were used at R1 R, and R4 in addition In this case the claimed compounds bear little structural resemblance to one the ones actually prepared.

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make or use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-4, 6-16 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-18 of copending Application No. 10/513,848. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The species appear to be the same, see the 102(e) rejection above for some examples of the hundreds of species.

11. Claims 1-4, 6-16 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-11 of copending Application No. 10/578,490. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The species also appear to be the same or very minor variants.

12. Claims 1-4, 6-16 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-5, 27-28 of copending Application No. 10/537,217. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The species also appear to be the same or very minor variants.

13. Claims 1-4, 6-16 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-8 of U.S. 7,381,840.

The subject matter claimed in the instant application and the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The species also appear to be the same or very minor variants.

Conclusion

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Monday-Friday 9:00 A.M. to 6:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David K. O'Dell/
Examiner, Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625